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Second Thyroid Neoplasms After Prophylactic Cranial Irradiation for Acute Lymphoblastic Leukemia

Yves Perel,[1]* Guy Leverger,[2] Anne Carrere,[1] Michel Caudry,[3] Erea Noel Garabedian,[4] Sophie Ansoborlo,[1] and Pierre Vergnes[5]

[1]Unit of Hematology and Oncology, Department of Pediatrics, Children's Hospital, Groupe Hospitalier Pellegrin, Bordeaux, France
[2]Unit of Hematology and Oncology, Department of Pediatrics, Children's Hospital Armand Trousseau, Paris, France
[3]Department of Medical Oncology and Radiotherapy, Saint-André Hospital, Bordeaux, France
[4]Department of Pediatric Surgery, Children's Hospital Armand Trousseau, Paris, France
[5]Department of Pediatric Surgery, Children's Hospital, Groupe Hospitalier Pellegrin, Bordeaux, France

An understanding of the pathogenesis of second cancers may help in their prevention. We report on two children who were treated for acute lymphoblastic leukemia (ALL), with an exclusively cranial prophylactic irradiation (18 Gy) and who presented with a thyroid carcinoma (TC) 12 and 13 years later. From a thorough review of the literature of TC after ALL and of radiation-induced TC, a strong case can be made that these tumors are caused by late effects of scattered radiation. The risk is at its highest in small children. After cranial irradiation, patients require clinical monitoring of the thyroid and cervical area for nodules, continued indefinitely. We suggest that, in most cases, an alternative form of neuromeningeal prophylaxis should be offered in small children with ALL. Am. J. Hematol. 59:91–94, 1998.

Key words: acute lymphoblastic leukemia; second neoplasm; thyroid carcinoma irradiation; radiation-induced

INTRODUCTION

With current strategies, 60 to 70% of cases of acute lymphoblastic leukemia (ALL) in children are cured. In these patients, there are six to seven times more new cancers (mostly brain tumors and acute leukemias) than would normally be expected, given the epidemiological data [1]. The actuarial estimated cumulative proportion of children in whom a second cancer developed is 2.53% at 15 years from diagnosis [1] but this figure is much less than the 7% rate of second cancers reported after Hodgkin's disease [2].

Thyroid carcinomas (TC) account for less than 1% of malignant disorders in children with an incidence of 0.3–$3/10^6$ in the population under 15 years of age [3]. When they occur as second cancers after solid cancers, TC are consistently associated with cervical irradiation [2,4].

We report on observations of two TC in children who had previously received exclusively cranial prophylactic radiotherapy, using the technique described by Pinkel and Woo [5]. In theory, a genetic predisposition or the treatment itself may affect the genesis of this second tumor and we put forward the hypothesis that scattered radiation may be responsible.

CASE 1

A 1-year-old girl was diagnosed as suffering from an ALL, L_1 according to French-American-British (FAB) classification, immunological type pre-B, common acute lymphoblastic leukemia antigen (CALLA) positive. Treatment consisted of vincristine, prednisone, asparaginase, and intrathecal therapy. Cranial radiation treat-

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*Correspondence to: Dr. Yves Perel, Hematology and Oncology Unit, Children's Hospital, Groupe Hospitalier Pellegrin, Place Amélie-Raba-Léon, 33076 Bordeaux Cedex, France. E-mail: yves.perel@chu-aquitaine.fr

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ment, which was for prophylactic purposes only, was delayed (until the infant was three years old) to limit neuropsychological toxicity. Eighteen Grays (Gy) cobalt 60 therapy were delivered in nine fractions by two opposed lateral fields including the floor of the anterior cranial fossa, the retro-orbital spaces and optic tracts, the temporal lobes and sphenoid sinus, and the base of the skull; the lower margin was established at the lower edge of the second cervical vertebra.

No recurrence of the leukemia, no abnormality in growth, puberty, or development occurred.

At the age of 16, a large, poly-lobed cervical mass began to develop. A biopsy revealed lymphatic metastases of papillary TC. A total thyroidectomy was performed with lymphadenectomy of bilaterally invaded jugulo-carotidian lymph nodes and mastoid nodes; surgery was complicated by a compressive long-standing chylothorax. A 150 mCi of ^{131}I radioiodine ablation therapy was delivered and scanning revealed that a residual tumor persisted in one upper mediastinal node. Six months later a second radioiodine treatment was performed; it was noted that the residual tumor tissue had disappeared. The ALL has now been in complete remission for 15 years and the TC for one year.

There was no family history of hemopathy, carcinoma, or any other thyroid disorder.

CASE 2

A four-year-old boy was diagnosed as having a non-T ALL, L_1 according to FAB, immunological type non-T. Treatment included prednisone, vincristine, daunorubicin, cyclophosphamide, asparaginase, and intrathecal therapy. After complete remission was achieved, cranial radiotherapy was administered as a purely preventive measure; a total of 18 Gy were administered in nine sessions of cobalt 60 by two opposed lateral fields including the floor of the anterior fossa, the posterior orbit and optic tracts, the temporal lobes, sphenoid sinus, and the base of the skull; the lower margin was established at the lower edge of the second cervical vertebra.

The child's general and hematological condition evolved favorably until the age of 16 when a 2 cm nodule appeared at the front of the neck which was hypoechoic. Pathological examination showed both a benign thyroid adenoma and a papillary TC of the thyroid isthmus which was invading the capsule. A total thyroidectomy was then performed. Pathological study revealed no metastatic extension onto the cervical nodes and the body scan after one dose of radioactive iodine therapy (150 mCi ^{131}I) was also negative. The ALL has now been in complete remission for 13 years and the TC for 1.5 years.

There were no other cases of thyroid disorders, leukemia, or cancer in the family.

DISCUSSION

Several registers demonstrate fairly conclusively that an association does exist between ALL and secondary TC: Of 329 second tumors reported by Kaatsch and Michaelis [6], 94 occurred after ALL and of these, nine were thyroid carcinomas. Meadows et al. [7] reported 411 second tumors, 35 occurred after ALL, and of these, seven were TC.

With a 4.7 years median period of follow-up, three TC were diagnosed among 9,720 ALL patients enrolled in the prospective study of Neglia et al. [1]. In only a few studies [8–12] are the characteristics of patients presenting with TC after ALL described (Table I). We have not mentioned a case of medullary TC [13], cases of TC observed after total body irradiation and bone marrow transplantation [14,15], or discovered only on postmortem examination [16]. All the patients were given radiation treatment as a preventive measure; six had cranial radiation only.

The dose received by the thyroid from scattered radiation during a 1,800–2,400 cGy cranial radiation varies between 13 and 132 cGy [17], which is less than the 200 cGy threshold described by Tucker et al. [4], beyond which they noted a significant risk of second TC in children receiving therapeutic radiation treatment. In several series of children irradiated mainly for benign disorders (tinea capitis, thymic, or tonsillar hypertrophy), the risks of TC which are already perceptible at 10 cGy in the youngest children, increase linearly according to the dose administered. The increase in relative risk is 7.7 Gy administered to the thyroid [18], and this clearly affects children receiving prophylactic cranial radiation. Beyond 10–20 Gy, the risk continues to increase with the dose, but to a lesser degree than with the linear model, and this could indicate that the phenomenon of blast killing occurs [5,18]. The risk is lessened if the radiation is fractionated [18]. In the case of cranial radiation, the diffused dose received by the thyroid can be decreased by using high-energy X-ray generated by linear acceleration [17], but a TC has nevertheless been reported after this type of radiation (Table I) [12]. It has been suggested that concomitant hypophyseal irradiation [17] or treatment in association with dactinomycin [4] may favor the occurrence of these TC, but this has not been proved, nor is the protection provided by the administration of thyroid hormones recognized universally [19].

TC after ALL occur in children who were very young when they received radiation—all were under six years old—all those who had only cranial radiation were under five years old. (Table I). There is clearly an inverse linear relationship between the age when radiation was given and the risk of second TC [4,7,18]. The risk is at its highest when the child is a baby, it decreases consider-

TABLE I. Patients' Characteristics; Second TC After ALL*

Cases [Ref.]	Sex	Age (years) (at the time of radiotherapy)	RT-TC interval (years)	RT Cranial dose (Gy)	RT Spinal dose (Gy)	RT source	Histology
1 [8]	M	1.7	6	24	0	Co	PTC
2 [9]	F	5.5	6.5	24	24	Co	FTC
3 [10]	F	1.7	5.5	18	18	Co	PTC
4 [10]	ns	1.1	5.5	18	0	Co	PTC
5 [10]	ns	1.9	10.2	24	0	Co	FTC
6 [11]	ns	4	14	Dose ns	Dose ns	Co	TC
7 [12]	F	2.7	10.5	22.5	0	Ph	TC
8 (Case 1)	F	3	13	18	0	Co	PTC
9 (Case 2)	M	4.5	11.6	18	0	Co	PTC
Total	4 F	2.7	10.2	18 Gy: n = 4	0 Gy: n = 6	8 Co/1 Ph	5 PTC
	2 M	(median)	(median)	>18 Gy: n = 4	>0 Gy: n = 3		2 FTC

*M, male; F, female; ns, not specified; RT, radiotherapy; Co, Cobalt 60; Ph, Photons 4 MV; PTC, Papillary thyroid carcinoma; FTC, Follicular thyroid carcinoma; TC, thyroid carcinoma; ALL, acute lymphoblastic leukemia.

ably after the age of five, and is no longer significant after the age of 40, or even after the age of 15 [18]. The particular risk involved in cranial radiation in a young child is attributed to the relatively short facial cranium [17] and the rapid proliferation of thyroid cells at that age.

The prevalence of *ret* oncogene in radiation-induced TC in children is high [19]; the occurrence of TC may in certain cases be a response to an ethnic or family susceptibility [19,20]. In the series of children receiving cervical radiotherapy for a first cancer, those with a neuroblastoma appeared to be particularly susceptible to a second TC [21]. Observed cases of TC after ALL were rare (3/43,466 person-years of follow-up) [1]. Conversely, epidemiological surveys reveal no excessive occurrence of ALL after TC [22]. Thus, there is no argument to support the hypothesis of a common mechanism for the occurrence of these two disorders.

Evidence of thyroid carcinoma after a dose of 10 to 100 cGy indicates that the thyroid has an extremely high level of radiosensitivity. The only way to avoid this risk in small children is to dispense with radiotherapy completely; however, the risks of this procedure (including thyroid carcinoma) need to be balanced with its specific oncological benefits. In children with B-precursor ALL, B-cell ALL, T-cell ALL with initial white blood cell (WBC) counts less than $50.10^9.1^{-1}$, extended intrathecal chemotherapy and intensive systemic chemotherapy is as effective as radiation for prevention of meningeal relapse (4% meningeal relapse rate) [5]. Because of the risk of TC, prophylactic cranial radiation should be strongly avoided. In patients with T-cell or lymphomatous ALL with WBC counts above $50.10^9 1^{-1}$ (most of them adolescents), cranial irradiation has been reported as more effective than other neuromeningeal prophylaxis (9% vs. 27%, five-year actuarial meningeal relapse rate) [23]. If this method is used, X-ray diffusion should be reduced to the minimum dose [5,17].

TC will continue to occur in subjects irradiated during childhood for ALL, with a considerable latency period (Table I). The incidence of second TC is reported to reach its maximum between 15 and 19 years after radiation [18]. These TC, if identified at an early stage, are highly curable malignancies. For patients in whom thyroid irradiation has occurred as a result of the diffusion of cranial radiotherapy, the very small risk of cancer [24] requires clinical monitoring of the thyroid and cervical area for nodules, but these checks should nevertheless be continued indefinitely.

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